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BLOOD PRESSURE PATTERNS AND SUBSEQUENT CORONARY ARTERY CALCIFICATION IN WOMEN WHO DELIVERED PRETERM BIRTHS

Janet M. Catov, PhD, MS^{1,2}; Gabrielle G. Snyder, MPH²; Abigail Fraser, PhD³; Cora E. Lewis, MD, MSPH⁴; Kiang Liu, PhD⁵; Andrew D. Althouse, PhD⁶; Marnie Bertolet, PhD²; Erica Gunderson, PhD, MS, MPH⁷

¹Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine & the Magee-Womens Research Institute, Pittsburgh, PA, USA

²Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, PA

³School of Social and Community Medicine, University of Bristol, UK

⁴Division of Preventive Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

⁵Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

⁶Vascular Institute, Department of Cardiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

⁷Division of Research, Kaiser Permanente, Oakland, CA, USA

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Corresponding author: Janet M. Catov, 204 Craft Avenue, Suite 2315, Pittsburgh, PA 15213, Telephone (412) 641-6217, Facsimile (412) 641-1133, email catovjm@upmc.edu

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Abstract

Women who delivered preterm infants have excess cardiovascular disease, but vascular pathways linking these conditions are not understood. We considered that higher blood pressure over 25 years among women with preterm delivery may be associated with coronary artery calcification (CAC). The CARDIA study enrolled 1,049 black and white women with births between 1985 and 2010 (n=272 ever preterm [<37 weeks]; n=777 all term births [≥ 37 weeks]). Latent mixture modeling identified blood pressure trajectories across 20 years and these were related to CAC at years 20 and 25. Three systolic blood pressure (SBP) patterns were identified: low-stable (n=563, 53%), moderate (n=416, 40%), and moderate-increasing (n=70, 7%). Women with moderate-increasing SBP were more likely to have delivered preterm compared to those in the low-stable group (40% vs. 21%, $p<0.0001$) and they were more likely to have CAC (38.5% vs. 12.2%). The SBP and CAC association varied by preterm birth (p -interaction=0.04). Women with preterm delivery and a moderate-increasing SBP had a 2.17-fold higher hazards of CAC (95% CI 1.14, 4.12) compared to women with term births and a lower SBP pattern, adjusted for CVD risk factors and other pregnancy features. There was no excess CAC in women with moderate-increasing SBP and term births (adjusted HR 1.02 [0.49, 2.14]). Associations were stronger in women with hypertensive disorders of pregnancy, but also detected in those with normotensive preterm deliveries. Women who deliver preterm infants are more likely to follow a high-risk blood pressure pattern throughout the childbearing years that is associated with CAC at midlife.

Key Words: Hypertension, Coronary artery calcium, Preterm birth, Atherosclerosis, Women

Introduction

Maternal history of preterm delivery (PTD) identifies excess cardiovascular morbidity and mortality for women,¹⁻⁴ but mechanisms linking preterm birth to the emergence of cardiovascular disease (CVD) are not well understood. Compared to women with term births, those with PTD have modestly higher blood pressure before, during, and after pregnancy,⁵⁻⁹ but the long-term associations of these differences with future CVD risk are unknown.

Non-pregnant longitudinal blood pressure measurements in men and women over 25 years reveal that increasing blood pressure patterns are associated with coronary artery calcification (CAC) in middle age.¹⁰ Similarly, the accumulation of exposure to modest elevation in blood pressure across adulthood (for example, systolic above 115 or 120 mmHg) is linked to excess cardiovascular risk.^{11,12} Indeed, the newest guidelines classify stage 1 hypertension as blood pressure at or above 130/80 mmHg, although treatment is not recommended at this lower threshold unless 10-year predicted CVD risk is 10% or higher.¹³ Women have lower blood pressure than men across adulthood.¹⁴ They are therefore over-represented in low risk blood pressure trajectories. Herein we focus on women across the childbearing years, and consider that adverse pregnancy outcomes such as preterm birth history could help identify women with blood pressure patterns representing excess risk for CVD.

CARDIA is one of the few longitudinal cohorts in which blood pressure was measured before and after pregnancy, and we have reported that women with preterm delivery had a modestly higher blood pressure compared to women with term births before pregnancy (2 mmHg) and after 20 years of follow up (4 mmHg). Indeed, differences in blood pressure increased more dramatically over time compared to women with term births, even among those with normotensive preterm births.⁶ How the vascular burden of modest blood pressure

increments might accumulate across the life course among women who deliver preterm pregnancies is unknown. To examine this, we first characterized blood pressure patterns across 20 years from young adulthood to midlife in women with at least one birth, and hypothesized that women with preterm as compared to term births would be more likely to follow a high-risk BP pattern. We then considered whether these blood pressure patterns were related to coronary artery calcification (CAC) at midlife and whether these associations were similar in women with preterm as compared to full-term births.

Methods

Study materials, data, and samples from CARDIA are available at <https://www.cardia.dopm.uab.edu/> and through the NHLBI BioLINCC program at <https://biolincc.nhlbi.nih.gov/home/>.

Coronary Artery Risk Development in Young Adults (CARDIA) is a U.S. multi-center, longitudinal, observational study designed to describe the development of risk factors for coronary heart disease in young black and white men and women.^{15,16} Participants were recruited from four U.S. areas: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. From 1985-1986, 5,115 subjects (2,787 women; 52% black) aged 18 to 30 years were enrolled and provided written informed consent. Retention rates were 92, 86, 81, 79, 74, 72, and 72 percent of the surviving cohort at years 2, 5, 7, 10, 15, 20, and 25 after baseline.

Of the 2,787 women enrolled in CARDIA we excluded women with hysterectomy at baseline (n=25), those who did not deliver live births between baseline and year 25 of follow up (n=1,377) and those with fewer than 4 visits with BP measurements (n=69; Supplemental Figure S1). Women with twin births or births with no reported gestational age were also excluded

(n=81). Of those remaining (n=1,232) we further limited our analysis to women with coronary calcium assessed at year 20 or 25. Eligible women with CAC measurements (n=1049) compared to those with no CAC measures (n=183) were about a year older at baseline, were less likely to be of African American race, had higher levels of education and modestly lower triglycerides measured at baseline (Supplemental Table S1).

Pregnancies and Preterm birth status.

All births that occurred after enrollment (baseline) in CARDIA are included in this analysis. These were assessed at exams that occurred every 2-5 years, and for each post-baseline birth women reported the gestational age at delivery (weeks) and birth weight. Preterm births were those delivered <37 completed weeks. A validation study compared maternal report of gestational age to medical record abstractions (n=211). Maternal report of ever delivering preterm (<37 weeks) was good (sensitivity was 84% [16/19]; specificity was 89% [170/192]).⁶ Women were categorized into two exposure groups: those who ever experienced a PTD and those with all term births.

Women also reported if each birth was complicated by gestational diabetes (GDM) or hypertensive disorders of pregnancy. Self-report of GDM history was excellent (100% sensitivity and 92% specificity).¹⁷ Self-reported hypertensive disorders of pregnancy were over-reported (positive predictive value was 42%) but the negative predictive value of self-report of no preeclampsia or gestational hypertension was 90%.¹⁸ Thus, while our study cannot definitively identify women with hypertensive disorders of pregnancy, we can be assured that the group reporting normotensive births were very likely to have been normotensive during pregnancy. Parity status (number of births) prior to baseline was assessed at enrollment.

Coronary artery calcium

Calcified coronary artery plaque was measured at years 20 or 25 using computed tomography (CT) of the chest.¹⁹ Briefly, at year 20 an electron-beam CT scanner (at Chicago and Oakland centers) and a multidetector CT scanner (at Birmingham and Minneapolis centers) were used to obtain contiguous 2.5 to 3 mm thick transverse images from the root of the aorta to the apex of the heart. At year 25, all centers used the multidetector CT scanner. The accuracy, comparability and reproducibility of CAC measurement is excellent.^{19,20} Scans were obtained and image analysts blinded to participant characteristics calculated a total coronary artery calcium score using a modified Agatston method,²¹ with select over-reading by a physician expert in cardiovascular imaging. The presence of CAC was defined as a total calcification score greater than 0 Agatston units measured at year 20 or 25 given the low prevalence of advanced calcification among women. Results were replicated when CAC was defined as ≥ 10 Agatston units.

Blood Pressure

Blood pressure was measured at baseline and each follow-up exam by standardized research methods.^{15,16} Three resting seated measurements were obtained with a random-zero sphygmomanometer through year 15 and with the Omron (Omron Corp., Schaumburg, IL) HEM907XL oscillometer at years 20 and 25; the mean of the second and third readings was used for this report. Omron results were calibrated to be consistent with the random-zero results.¹⁸ Systolic and diastolic blood pressure were analyzed separately for trajectory analyses. Mid-blood pressure (average of SBP and DBP) was also evaluated given the evidence that it may better predict CVD events than other composite measures such as pulse pressure or mean arterial pressure.^{22,23} Anti-hypertension medication or statin use was reported at each visit.

Other variables

Fasting blood samples were sent to the Northwest Lipid Research Laboratories (Seattle, WA, USA) for lipid determination within 6 weeks of collection.²⁴ LDL-cholesterol was calculated using the Friedewald equation when triglycerides were <400 mg/dl.²⁵ Height and weight were measured during each examination and used to calculate body mass index (BMI, kg/m²). Waist circumference was measured as the abdominal girth midway between the iliac crest and the bottom of the ribcage. Demographic characteristics (age, sex, and race) were obtained at baseline; educational achievement was self-reported on standardized questionnaires as was smoking status (nonsmoker, ex-smoker, and current smoker).

Statistical analysis.

Blood pressure trajectories were modeled for women with one or more births and at least 4 BP measurements from baseline through follow up. Latent class models identified subgroups of women with a similar underlying trajectory in BP using SAS Proc Traj (details provided in Supplement).²⁶

In order to maximize the sample size and avoid bias that may be introduced by requiring attendance at the year 25 visit, we first constructed BP trajectories through year 20 and related these to CAC detected at year 20 or Year 25. This approach also allowed early presence of CAC to be considered which was relevant to our hypothesis, as 73% of women had CAC measured at both time points. We used a variation of the Cox proportional hazards model that accounts for interval-measured data to estimate the relative hazards of CAC presence according to BP latent class.²⁷ Multivariable models adjusted for demographic characteristics (race, education, age), lifestyle features (time-varying BMI and smoking), medication use (anti-hypertensives and statins), and other pregnancy features (GDM and hypertensive disorders of pregnancy). Models were also adjusted for the posterior probability of being included in a trajectory to account for

the variability in class assignment. Additional adjustment for parity, lipids or baseline blood pressure did not change any estimates by >10%, and thus these were not included. We tested for a differential association between BP trajectories and CAC according to preterm birth history using a multiplicative interaction term ($p < 0.10$), and also tested for relative excess risk due to interaction on the additive scale as this may be more biologically plausible and of greater public health relevance (Relative excess risk due to interaction [RERI_{RR}] greater than 1).²⁸ Given evidence of effect modification on both scales, exposure groups that combined BP patterns and preterm birth history were evaluated. Women with term births and a low-stable or moderate BP pattern were the referent as the prevalence of CAC was similar in these groups (12.2 and 16.1%, respectively). We then modeled trajectories through year 25 to account for steeper increases in BP that may occur after year 20, and related these patterns to CAC presence at year 25 using logistic regression. Covariate adjustment was as above. Sensitivity analyses were conducted defining CAC as Agatston units ≥ 10 . We also stratified results by race, by hypertensive status (ever/never; defined as blood pressure $\geq 140/90$ mmHg or taking anti-hypertensive medication), and by self-reported hypertensive disorders of pregnancy (ever/never) to ensure that associations were similar in subgroups.

Results

Across 25 years of follow up, 272 women experienced preterm birth and 777 reported all term births. Women with preterm delivery history compared to those with all term births were more likely to be of Black race, less likely to have attended college, and had modestly higher systolic blood pressure at baseline which was prior to the births included in this analysis (Table 1). By year 25 women with preterm deliveries had higher systolic, diastolic and mid-blood

pressure, were more likely to report having experienced hypertension in pregnancy and to be using anti-hypertensive medications.

Three trajectories in systolic (SBP), diastolic (DBP) and mid-blood pressure (MBP) were identified (Figure 1): 53% of women maintained low SBP across follow-up (low-stable, n=563); 40% maintained moderate SBP (moderate, n=416); and 7% started with moderate SBP that increased rapidly after about 10 years of follow up (moderate-increasing, n=70). Trends were similar for diastolic and mid-blood pressure but most pronounced for systolic BP.

Women in the moderate-increasing SBP group were more likely to be of Black race and to have a higher BMI and waist circumference at baseline and after 25 years of follow up. They also were more likely to experience preterm birth and pregnancies complicated by hypertension compared to the low-stable SBP group (Table 2). After accounting for race, age, education, smoking, BMI and total cholesterol, women with PTD tended to be more likely to be in the moderate-increasing SBP group (OR 1.46, 95% CI 0.85, 2.49). As expected, women in the moderate-increasing SBP group were also more likely to have CAC at year 20 or 25; 38.6% of women in the moderate-increasing SBP trajectory had CAC compared to 13.5% of women in the low SBP trajectory ($p<0.0001$).

Among women with moderate-increasing SBP, those with preterm deliveries were more likely to have CAC than women with term births (p for multiplicative interaction =0.04; $RERI_{RR}=1.30$ for additive interaction; Figure 2). Women in the moderate-increasing SBP trajectory and a history of preterm birth had 2.17-fold higher hazards of CAC (95% CI 1.14, 4.12, $p=0.018$; Table 3) by year 25 compared to women with term births and low-stable or moderate SBP after accounting for covariates. In contrast, excess risk of CAC in women with a moderate-increasing SBP pattern and all term births was not detected (adjusted hazard ratio [HR]

1.02, 95% CI 0.49, 2.14; $p=0.952$). When restricted to those in the higher BP trajectory, women with PTD tended to have higher risk of CAC than women with full-term births, although this estimate was not statistically significant (HR 2.12, 95% CI 0.88, 5.09, $p=0.094$; Supplemental Table S2). Risk of CAC also tended to be higher when related to mid-blood pressure trajectories and preterm birth history (adjusted HR for moderate-increasing MBP and preterm birth, 1.85, 95% CI 0.97, 3.51, $p=0.061$) but was not higher for DBP trajectories.

Results were amplified when risk of CAC at year 25 was estimated according to BP trajectories through year 25 (Supplemental Table S3). Those in the moderate-increasing SBP trajectory had significantly increased risk of CAC and this was strongest in women with history of preterm birth (adjusted odds ratio [OR]=4.40, 95% CI 1.80, 10.75, $p<0.0001$). The associations were more modest in participants with only term births. The associations of SBP trajectories and preterm delivery persisted when presence of CAC was defined as ≥ 10 Agatston units, but were diminished for DBP and Mid-BP (Supplemental Table S4). Results were of similar magnitude but less precise in White and Black women (Supplemental Table S5). Results were also very similar significant, after removing women who were hypertensive at baseline ($n=20$).

We then stratified according to hypertension (ever vs. never) rather than BP trajectories. Women with hypertension and a history of preterm birth had higher risk of CAC compared to those with no hypertension (HR 2.76, 95% CI 1.29, 5.90), adjusted for covariates. Women with hypertension and term births also had excess CAC, but this risk was more modest compared to estimates in women with preterm deliveries (HR 1.62, 95% CI 0.96, 2.71, $P_{\text{interaction}} = 0.08$).

We further considered that preterm deliveries complicated by hypertensive disorders of pregnancy may be influencing our results. Those who reported a history of hypertensive

disorders of pregnancy and an increasing SBP trajectory had excess CAC risk, regardless of preterm delivery (HR 3.40 [1.18, 9.74] for term births; HR 3.59 [1.31, 9.79] for preterm births; Supplemental Table S6). Women with normotensive preterm births and increasing SBP also had excess CAC risk (HR 2.45, 95% CI 0.97, 6.23). In contrast, those with an increasing SBP trajectory but all normotensive term births had no excess CAC.

Discussion

Our results indicate that women with preterm deliveries combined with an increasing BP trajectory had particularly strong risk of coronary artery calcification that was independent of other traditional CVD risk factors and pregnancy complications. In contrast, CAC risk tended to be smaller among women with term births and an increasing BP trajectory. Of note, women with preterm deliveries were also more likely to follow an increasing blood pressure pattern compared to women with term births. Our results highlight the importance of race in these associations. Black women were much more likely to have preterm deliveries, to follow an increasing blood pressure pattern, and to have CAC. The average age of women at the end of follow up was less than 50, and thus most women were at overall low risk for CVD. Preterm birth may identify women with high risk of increasing blood pressure and progression to atherosclerosis quite early in the life course.

Early detection of hypertension or modest elevations in blood pressure is crucial, as treatment is widely available, inexpensive and cardioprotective. Yet, up to 38% of hypertension goes undetected before age 40.²⁹ Importantly, hypertension contributes to more CVD events in women relative to men.³⁰ There is also evidence that the accumulation of modest blood pressure elevation over young adulthood is linked to atherosclerosis, left ventricular mass, and vascular mortality.^{11,12} Our data suggest that at an average age of 24 at

baseline, women with modestly higher BP go on to follow an elevated trajectory and thus modest BP elevations in young adulthood may warrant closer clinical attention. Our results indicate that preterm birth history may identify a subgroup of women susceptible to increasing blood pressure and higher risk for development of atherosclerosis. It is unknown if preventing the preterm birth may also prevent maternal progression to CAC, but our results amplify the importance of preterm birth for maternal long-term health. Recent evidence indicates that presence of any CAC, including those with low scores as we include here, is linked to coronary heart disease events and death.^{31,32} Indeed, some have called for the inclusion of CAC screening to stratify women and men for treatment.³³ Our results raise important questions about how pregnancy history may help inform CVD screening and treatment guidelines for women.

There are few studies of the vascular pathways linking preterm delivery to CVD. Our results are aligned with evidence from the Nurses' Health Study that women with preterm deliveries have excess CVD risk, not explained by obesity, lifestyle or sociodemographic risk factors.³⁴ Our findings raise the possibility that there may be novel endothelial factors leading to increasing BP and CAC in women with preterm deliveries. Alternatively, it is possible that the modest elevations in BP detected even before preterm births may be related to occult inflammation or oxidative stress³⁵ that instigate vascular remodeling, culminating in arterial plaque formation by age 50. Recent work has identified maternal genes related to blood pressure control, carotid intima-medial thickness and metabolic risk that are also related to preterm delivery.³⁶ In addition, familial aggregation of PTD may have developmental origins, such that women who themselves were born small or preterm may have excess risk of preterm delivery as well as hypertension and CVD.^{37,38} We did not collect information about a mother's own birth history, but future work should explore these associations.

Our results must be considered in the context of study limitations. CARDIA is a large, bi-racial cohort and yet the number of women with CAC is still small. Longer follow up is needed to accrue more events and to understand if preterm delivery history discerns risk across the aging continuum. It is possible that reproductive features can best identify risk among pre-menopausal women.⁷ CAC was not measured at baseline and thus we were unable to determine if women in the highest BP trajectory group or those with preterm birth may have had prior CAC. We also relied upon self-report of pregnancy complications. Although our validation study demonstrated good recall of preterm birth, studies with medical record data are needed to determine if subtypes of preterm birth such as spontaneous preterm birth or clinically indicated early delivery may be driving the risk estimates we detected. While this may hamper the etiologic interpretation of our findings, our results suggest that reliably recalled pregnancy features such as preterm delivery can mark excess CVD risk in women. Maternal recall of hypertensive disorders of pregnancy in our study, similar to others, was poor. The high negative predictive value of maternal recall of this complication, however, does reassure us that our findings in women having reported normotensive preterm deliveries are robust. In addition, future studies are needed to understand the timing of blood pressure changes relative to each birth. Self-reported preterm deliveries prior to the baseline visit were missing for many women, and therefore we were unable to consider these in our analysis. Most women in CARDIA were nulliparous at baseline (70%), and thus this may only modestly affect our estimates. Strengths of our study include the substantial number of Black women, as preterm birth and CVD disproportionately affect this group. We also could evaluate a long continuum from before pregnancy through 25 years of follow up with robust measurements of blood pressure and pregnancy history. In contrast to pregnancy cohorts that study a single birth, we described the entire pregnancy history after enrollment in CARDIA. As a result, the

preterm birth rate in this bi-racial childbearing cohort was high and thus an ideal population in which to study these associations.

Perspectives

Our results provide evidence that women with preterm deliveries are more likely to follow an increasing blood pressure trajectory from before to many years after pregnancy compared to women who deliver all births at term. This high-risk blood pressure pattern combined with a history of preterm birth is associated with excess risk of coronary atherosclerosis that does not appear to be explained by traditional CVD risk factors. Preterm birth history coupled with higher blood pressure may identify women in whom further risk stratification may be warranted.

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Conflicts of Interest/Disclosures:

None.

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Novelty and Significance

What is New?

- Women with preterm deliveries are more likely to follow an increasing blood pressure pattern across 25 years
- Preterm birth together with an increasing blood pressure pattern is associated with excess risk of coronary artery calcification, a strong predictor of CVD
- These patterns persisted when limited to women with normotensive preterm births

What is Relevant?

- Preterm birth is reliably reported by women, and could identify a group who may benefit from blood pressure surveillance
- Blood pressure elevations in women with a prior preterm birth may mark excess risk for coronary artery calcification

Summary

Preterm birth may identify women who are susceptible to hypertension and subclinical atherosclerosis.

Figure 1. Systolic blood pressure trajectory (Panel A) across 20 years in women with at least one birth in CARDIA; Low-stable (green, n=563); Moderate (blue, n=416) and Moderate-Increasing (red, n=70). Diastolic blood pressure trajectory (Panel B); Low-stable (green, n=425); Moderate (blue, n=513) and Moderate-Increasing (red, n=111). Mid-blood pressure trajectory; Low-stable (green, n=418); Moderate (blue, n=500) and Moderate-Increasing (red, n=131).

Figure 2. Proportion of women with CAC at year 25 according to Systolic, Diastolic and Mid-Blood Pressure trajectories (Green [low-stable trajectory]; Blue [moderate trajectory]; red [Moderate-increasing trajectory]) and stratified by term and preterm birth status.

Table 1. Characteristics of women at baseline and during follow up according to preterm birth status*

	Baseline			Year 25		
	Term (N=777)	Preterm (N=272)	P- value	Term (N=777)	Preterm (N=272)	P-Value
Maternal Characteristics						
Black (%)	40.5	66.9	<.0001			
Nulliparous (no prior births, %)	71.4	65.8	0.082			
Parity	0.4 ± 0.8	0.5 ± 0.9	0.042	1.7 ± 0.8	2.0 ± 1.1	0.0001
Education (%)			<.0001			0.004
High school or equivalent	29.4	44.9		16.6	27.2	
College Education	58.8	50.7		54.2	56.3	
Graduate or Professional Degree	11.8	4.4		29.2	16.5	
Age (years)	24.3 ± 3.7	23.6 ± 3.6	0.007	49.4 ± 3.7	48.8 ± 3.6	0.017
Current smoking (%)	22.3	28.4	0.065	12.1	19.9	0.009
Body Mass Index (kg/m ²)	23.5 ± 4.8	24.0 ± 5.0	0.095	29.4 ± 7.4	31.4 ± 7.7	0.0003
Waist Circumference (cm)	72.2 ± 9.8	72.6 ± 10.3	0.599	88.9 ± 15.9	91.7 ± 15.6	0.018
Systolic Blood Pressure (mmHg)	105.2 ± 9.2	106.5 ± 8.7	0.038	115.2 ± 15.0	120.5 ± 17.9	<.0001
Diastolic Blood Pressure (mmHg)	65.9 ± 8.9	65.7 ± 9.0	0.726	72.6 ± 11.5	76.0 ± 11.9	<.0001
Mid-Blood Pressure (mmHg)	85.6 ± 8.0	86.1 ± 7.6	0.320	93.9 ± 13.4	98.3 ± 14.4	<.0001
Total Cholesterol (mg/dl)	177.1 ± 31.5	177.3 ± 34.2	0.924	193.3 ± 34.1	193.9 ± 39.6	0.834
LDL Cholesterol (mg/dl)	108.4 ± 29.3	107.7 ± 31.1	0.745	109.8 ± 29.8	112.8 ± 34.6	0.220
HDL Cholesterol (mg/dl)	55.6 ± 12.4	57.5 ± 13.3	0.037	63.6 ± 18.6	61.9 ± 18.8	0.200
Triglycerides (mg/dl), median(IQR)	58 (33)	56 (31)	0.034	84 (57)	80.5 (53)	0.350
Fasting Glucose (mg/dl)	79.6 ± 8.3	79.9 ± 8.6	0.567	94.8 ± 22.5	95.8 ± 25.2	0.556
During Follow Up						
Gestational diabetes mellitus (GDM), ever (%)				11.5	11.8	0.890
Hypertension during pregnancy, ever (%)				12.2	19.1	0.005
Anti-hypertensive medication use (%)				20.3	28.6	0.007
Statin use (%)				11.3	11.2	0.994

*Mean ± SD unless otherwise noted

Table 2. Characteristics of CARDIA women according to systolic blood pressure trajectory groups at Year 20

	Low (N = 563)	Moderate (N = 416)	Elevated (N = 70)	P-value
Maternal Characteristics				
Baseline				
Age at enrollment (years)	24.3 ± 3.7	23.7 ± 3.7	25.1 ± 3.3	0.004
Black (%)	31.6	63.2	80	<.0001
Parous (%)	25.6	32.7	50	<.0001
Education (%)				<.0001
High school or equivalent	28.1	37.7	50.0	
College	59.3	55.3	44.3	
Graduate or Professional	12.6	7.0	5.7	
Blood Pressure and Other Cardiovascular Risk Factors				
Never Smoking (%)				
Baseline	62.5	65	53.6	0.0002
Year 25	66.7	65.3	58.8	0.0075
Body Mass Index (kg/m ²)				
Baseline	22.4 ± 3.6	24.7 ± 5.5	26.8 ± 6.5	<.0001
Year 25	28.0 ± 6.5	32.0 ± 7.8	33.4 ± 8.8	<.0001
Waist Circumference (cm)				
Baseline	70.0 ± 7.5	74.2 ± 10.8	79.4 ± 15.0	<.0001
Year 25	85.2 ± 13.6	94.4 ± 16.5	97.9 ± 17.4	<.0001
Systolic Blood Pressure (mmHg)				
Baseline	101.0 ± 7.1	109.6 ± 7.6	117.7 ± 9.5	<.0001
Year 25	109.3 ± 12.6	123.0 ± 15.3	137.6 ± 21.4	<.0001
Diastolic Blood Pressure (mmHg)				
Baseline	63.4 ± 7.9	68.2 ± 8.7	72.3 ± 11.2	<.0001
Year 25	68.7 ± 9.8	78.1 ± 10.5	85.4 ± 13.5	<.0001
Mid-Blood Pressure (mmHg)				
Baseline	82.2 ± 6.5	88.9 ± 6.9	95.0 ± 9.2	<.0001
Year 25	89.0 ± 10.7	100.5 ± 12.3	111.5 ± 16.5	<.0001
Total Cholesterol (mg/dl)				
Baseline	175.6 ± 31.1	178.7 ± 31.9	180.4 ± 41.9	0.200
Year 25	195.4 ± 34.6	190.8 ± 35.6	193.4 ± 42.6	0.147
During Follow up				
Preterm birth (<37 weeks; %)	21.0	30.3	40.0	<.0001
GDM ever (%)	11.2	11.8	12.9	0.900
Hypertension during any pregnancy (%)	6.0	20.0	42.9	<.0001
Anti-hypertensive medication use (%)	4.5	36.6	80.9	<.0001
Statin use (%)	6.1	16.2	23.9	<.0001
CAC presence at year 25(%)	13.5	19.2	38.6	<.0001

P-value derived from ANOVA or chi-square; results are mean \pm SD unless noted; GDM, gestational diabetes mellitus; CAC, Coronary artery calcification

Table 3. Blood pressure trajectories through year 20 and preterm birth history, related to hazards of coronary artery calcification at year 20 or 25 (n=1,049)

Group	CAC N	95%			
	(%)	HR	CI		p
Term birth, Low-stable or Moderate SBP Trajectory	117 (15.9)	Ref			
Preterm birth, Low-stable or Moderate SBP Trajectory	39 (16.0)	0.75	0.47	1.18	0.215
Term birth, Moderate- Increasing SBP Trajectory	14 (33.3)	1.02	0.49	2.14	0.952
Preterm birth, Moderate-Increasing SBP Trajectory	13 (46.4)	2.17	1.14	4.12	0.018
Term birth, Low-stable or Moderate DBP Trajectory	111 (15.9)	Ref			
Preterm birth, Low-stable or Moderate DBP Trajectory	43 (18.0)	0.88	0.57	1.35	0.556
Term birth, Moderate-Increasing DBP Trajectory	20 (25.0)	0.90	0.50	1.64	0.733
Preterm birth, Moderate-Increasing DBP Trajectory	9 (29.0)	1.21	0.52	2.78	0.658
Term birth, Low-stable or Moderate MBP Trajectory	103 (14.8)	Ref			
Preterm birth, Low-stable or Moderate MBP Trajectory	37 (16.5)	0.84	0.53	1.33	0.448
Term birth, Moderate-Increasing MBP Trajectory	28 (33.7)	1.36	0.80	2.33	0.259
Preterm birth, Moderate-Increasing MBP Trajectory	15 (31.3)	1.85	0.97	3.51	0.061
Adjusted for Age at baseline, Race, Education, Years smoking, Statins, Hypertensive medication use, posterior probability of SBP group assignment and time-varying BMI, Gestational hypertension and GDM					